(b) amino acids 1 through 194.

REMARKS

Reconsideration and allowance in view of the foregoing amendments and the following remarks are respectfully requested.

Claims 1-11, 14, 27-29, 31-34 and 36-51 are presently pending in this application. Claims 1-11, 14, 27-29, 31-34 and 36 are withdrawn from consideration and claims 40-51 are being prosecuted. By this Amendment, claims 40, 48, 49 and 50 have been amended and claim 45 has been canceled. Claim 40 has been amended by deleting "for use in securing expression in a procaryotic or eucaryotic host cell" from the preamble. Claims 40, 49 and 50 have been amended to conform with standard Markush language.

Claims 40 and 49 have also been amended to specifically recite "wherein said cysteine residues are selected from the group consisting of amino acid positions 1, 13, 72, 101, 126, 128, 133, 138, 146, 167 and 175 in Figure 2". Specific support for this amendment can be found in Figure 2. In addition, the specific recitation of claim 45 that the cysteine residues are replaced by alanine or serine has been incorporated into each of the claims. Accordingly, claim 45 has been canceled.

Claims 40 and 49 have also been amended to specifically recite "wherein said tyrosine residues are selected from the

group consisting of amino acid positions 36, 45, 64, 84, 122, 139 and 178 in Figure 2". Specific support for this amendment can be found in Figure 2. Finally, "transfected" has been deleted from claim 48. Thus, no new matter has been added by any of these amendments.

Rejections Under 35 USC 112, Second Paragraph

On pages 2-3 of the Official Action of February 15, 1996, the Examiner rejects claims 40-51 under 35 USC 112, second paragraph, as being vague and indefinite. In this rejection, the Examiner states:

> Claims 40-51 are vague and indefinite in their recitation of "DNA for use in securing expression", "selected from among", "wherein one or more cysteine residues is deleted or replaced by another amino acid", "a polypeptide of subpart (a) or (b) wherein one or more cysteine residues is deleted or replaced by another amino acid", "a polypeptide of subpart (a) or (b) wherein one or more tyrosine residues is replaced by phenylalanine", and "a polypeptide of any of subparts (a), (b), (c) or (d), lacking residues -26 through -1, and having a methionyl residue at position -1", and/or "has at least one cysteine residue replaced by an amino acid selected from alanine and serine". What does "for use in securing expression mean"? Do applicants intend that the DNA encodes the polypeptides(s) of figure 2? With regard to method claims, do applicants intend co-transfection? "Selected from among" is improper Markush language. Which cysteine residues are replaced? Which amino acids are they replaced with? Which cysteine residues are deleted? Which residues are replaced? Which cysteine residues are replaced with alanine or serine. Attention is directed to Ex parte Tanksley (26 USPQ2d 1384) wherein the Board noted that, under 35 USC 112, second paragraph, the claims must be so definite as to allow their comparison with the available art and must

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> also make it possible for the public to determine from the claims what it is they comprehend. It is asserted that a member of the public would not know what is intended by that which is claimed.

In an effort to advance the prosecution of this application and without acceding to the position of the Examiner, Applicants have amended claims 40, 48, 49 and 50. Claim 40 has been amended by deleting "for use in securing expression in a procaryotic or eucaryotic host cell" from the preamble. Claims 40, 49 and 50 have been amended to conform with standard Markush language. Claims 40 and 49 have also been amended to specifically recite the cysteine and tyrosine positions in the polypeptides. Also, the specific recitation that the cysteine residues are replaced by alanine or serine has been incorporated into each. In addition, claim 48 has been amended by deleting the word "transfected" from the claim.

In regard to the expression "a polypeptide of any of subparts (a), (b), (c) or (d), lacking residues -26 through -1, and having a methionyl residue at position -1", it is respectfully submitted that the expression is neither vague nor indefinite. The Examiner is directed to page 10, lines 30-32 of the specification for a description of polypeptides having an initial methionine, i.e., at position -1, and to page 43, lines 33-36 and to Figure 9 for a specific exemplification of this embodiment of the invention.

In view of these amendments and this explanation, it is respectfully requested that this rejection be withdrawn and that claims 40-44 and 46-51 be allowed.

Objections/Rejections Under 35 USC 112, First Paragraph

On pages 3-7 of the Official Action of February 15, 1996, the Examiner objects to the specification and rejects claims 40-51 under 35 USC 112, first paragraph. In the first part of this objection/rejection, the Examiner states:

> The specification is objected to under 35 U.S.C. § 112, first paragraph, as the specification, as originally filed, does not provide support for the invention as is now claimed.
>
> Specific basis is lacking in the specification for the recitation of "wherein one or more cysteine residues is deleted or replaced by another amino acid". Thus, the recitation is considered to be new matter. Moreover, applicants point to page 11 for support of their newly amended claims, however, page 11, at lines 21-21, merely sets forth that the cysteine residues may be <u>replaced by alanine or serine</u>. That is, the examiner cannot find support for the deleted cysteine residues or for the replacement of any cysteine residues by any amino acid. Please see MPEP 608.04 and 706.03(o).

In response, it is respectfully submitted that the Examiner's understanding of the specification is incorrect. Page 11, lines 20-21, states:

> ... which have one or more cysteine residues <u>deleted</u> or replaced by, e.g., alanine or serine residues .... (underlining added)

Thus, the specification clearly provides support for the deleted cysteine residues. In addition, claims 40 and 49 have

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been amended to specifically state that the cysteine residues are replaced by alanine or serine.

In the second part of this objection/rejection, the Examiner states:

> The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure.
>
> The scope of the claims is broader than the enablement provided by the specification. That is, variants of the instant enzyme inhibitor are claimed, however, the specification fails in teaching specific substituted or deleted polypeptides (or DNAs which encode said polypeptides) having the claimed characteristics. No guidance is provided as to which cysteine residues of the disclosed polypeptide can be modified without changing the activity. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the large number of polypeptides broadly encompassed by the claims. Predictability of which changes can be tolerated in a protein's amino acid sequence while retaining similar activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, the problem of predicting protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex (see the whole publication of Bowie et al. 1990. Science, Vol 247, pp. 1306-1310, particularly p. 1306 and column 2 of p. 1308).
>
> While recombinant and mutagenesis techniques are known and it is known that some proteins can tolerate a number of amino acid substitutions (i.e. predominantly in non-conserved amino acids), the positions within the protein's sequence where such amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited and such

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modifications are unpredictable in the absence of further guidance. Other positions in the sequence of such proteins are **critical** to the protein's structure/function relationship, e.g. such as various positions or regions directly involved in binding, catalysis or other activity and in providing the correct three-dimensional spacial orientation of binding and/or catalytic sites, and one skilled in the art would expect any tolerance of a given protein to modification to decrees [sic] with each further and additional modification, e.g. multiple substitutions. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acids modification in such proteins. However, even if it were shown that some modifications could be tolerated in the claimed DNAs encoding the polypeptide(s), for the reasons discussed the claims would still expectedly encompass a significant number of inoperative species which could not be distinguished without undue experimentation.

While enablement can be supported even if some experimentation is required, such experimentation must be merely routine and if the results to be obtained are unpredictable the experimentation is not routine, but rather **undue**. Applicants have not taught where the critical cysteine residues are in the instant polypeptide or related polypeptides having the same activity nor what amino acids are conserved in the particular claimed polypeptides nor the structural requirements for producing compounds of similar activity. See Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986). Recently, in Ex parte Maizel (27 USPQ2d 1662), the Board considered that claims encompassing such biologically functional equivalents were analogous to a single means claim and as such were more broad than the disclosure which disclosed only a single specific DNA segment known to the inventor. Such is the case here in which the specification is considered enabling only for claims limited to the specific nucleic acid sequence given in Figure 2.

In response, Applicants first note that claims 40 and 49 have been amended to specifically recite the cysteine and tyrosine positions in the polypeptides. Also, the specific

recitation that the cysteine residues are replaced by alanine or serine has been incorporated into each.

Second, case law provides that enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is "undue," not "experimentation". The determination of what constitutes undue experimentation in a case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 8 USPQ2d 1400, at 1404 (Fed. Cir. 1988).

In this regard, the specification teaches that the cysteine residues are located at amino acid positions 1, 13, 72, 101, 126, 128, 133, 138, 146, 167 and 175 in Figure 2. Furthermore, the specification provides specific guidance with respect to any experimentation. Assays for the measurement of the metalloproteinase inhibitory activity of the polypeptides of the present invention are given, for example, on page 18, line 16 to page 19, line 19, and on page 63 (Table 8) of the specification.

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It follows that a determination of biological activity in cysteine-modified polypeptides of the present invention would be a matter of mere routine experimentation.

Third, in regard to the number of DNA sequences disclosed in the specification, it is again respectfully submitted that the Examiner's understanding of the specification is incorrect. Figure 2 shows the cDNA sequence and amino acid sequence of human metalloproteinase inhibitor. Figure 9 shows a DNA containing an initiation methionine codon and codons for the first 42 amino acids of the mature metalloproteinase inhibitor protein. This DNA was constructed for use in the expression of recombinant human metalloproteinase inhibitor in *E. coli*, i.e., for polypeptides having an initial methionine (a methionine residue at position -1).

In view of the amendment of claims 40 and 49 and the above-given explanations, it is respectfully submitted that the specification and claims are in full compliance with the requirements of 35 USC 112, first paragraph. It is, therefore, respectfully requested that this objection/rejection be withdrawn and that claims 40-44 and 46-51 be allowed.

All objections and rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited.

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Should any matters remain in this application which might be resolve by interview, the Examiner is respectfully requested to telephone the undersigned at (202) 466-6300.

Respectfully submitted,

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